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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/737,290	12/15/2003	Katherine S. Bowdish	ALEX-P04-054	6650

28120 7590 02/21/2006

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/737,290	BOWDISH ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/11/2006.*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-9 in part, and 14, drawn to an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementary determining region (CDR) are replaced with an hBNP peptide or an hBNP peptide mimetic in the reply filed on 01/11/2006 is acknowledged.

The traversal is on the ground(s) that the groups set forth by the Examiner that Group I is closely related to the other groups (Groups I-VI), in particular, Group VII (claims 10-13, in part. Group VII is drawn to a nucleic acid encoding the immunoglobulin molecules or fragments thereof of Group I and a method for producing the immunoglobulin molecules or fragments thereof of Group I. Accordingly, searches related to the immunoglobulin molecules or fragments thereof, nucleic acids encoding same, and methods for producing the immunoglobulin molecules or fragments thereof are co-extensive, and simultaneous examination of the pending claims of Groups I and VII will not impose a substantial additional burden on the Examiner. Accordingly, Applicants respectfully elect Group I with traverse, but request that the inventions of Groups I and VII be rejoined and the reconsideration and withdrawal of the restriction requirement are respectfully requested. This is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate classification and search.

The applicant is reminded of the reasons as set the in the previous office action that the immunoglobulin molecule of Groups I-VI and the polynucleotide of Group VII are patentably distinct for the following reasons: The IgG molecule of Group I-VI consists of 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarily determining regions (CDRs). Polypeptides, such as the immunoglobulin molecule of Group I-VI which are composed of amino acids, and polynucleotide of Group VII, which are composed of nucleic acids, are structurally distinct molecules; any relationship between a polynucleotide and polypeptide is dependent upon the information provided by nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded polypeptide. Therefore, the antibody and polynucleotide are patentably distinct. The antibody and polynucleotide inventions have a separate status in the art as shown by their different classifications. Contrary to the applicants satatement that "searches related to the immunoglobulin molecules or fragments thereof, nucleic acids encoding same, and methods for producing the immunoglobulin molecules or fragments thereof are co-extensive, and simultaneous examination of the pending claims of Groups I and VII will not impose a substantial additional burden on the Examiner", searching the inventions of Groups I-VI and Group VII does would impose a serious search burden on examiner since a search of the immunoglobulin of Group I-VI would not be used to determine the patentability the polynucleotide of Group VII, and vice-versa. Thus, Groups I-VI and VII represent separate and distinct inventions. The record set forth in the previous restriction requirement clearly indicated

that the delineated inventions are in fact patentably distinct each from the other or independent from the other.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 10-13 and 15-22 are withdrawn from further consideration under 37 C.F.R. 1.142(b) as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply on 01/11/2006.

3. Claims 1-9 in part, and 14, drawn to an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementary determining region (CDR) are replaced with an hBNP peptide or an hBNP peptide mimetic read on the elected invention.

Priority

4. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications as listed in the first line of the specification, "U.S. application Ser. No. 10/452,590 filed Jun. 2, 2003, which is a

continuation-in-part of U.S. application Ser. No. 10/307,724 filed Dec. 2, 2002 which is a continuation-in-part of U.S. application Ser. No.10/006,593 filed Dec. 5, 2001 which claims priority to U.S. Provisional Patent Application No. 60/251,448 filed Dec. 5, 2000, and to U.S. Provisional Patent Application No. 60/288,889 filed May 4, 2001, and to U.S. Provisional Patent Application No. 60/294,068 filed May 29, 2001, fails to provide adequate support or enablement(hBNP or hBNP mimetic peptide) in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Hence the instant application (US 10/737,290) is granted the priority date of 12/15/2003 (the filing date of the instant filing date).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for reciting abbreviations "hBNP" in claim 1. Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

Further the instant claim is not clear for reciting "at least a portion of a complementary determining regions (CDRs) is replaced": Does it mean the applicant mean that the entire CDR is replaced or only a few amino acid residues within the CDR are replaced? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In addition, the claim is indefinite for reciting "a CDR is replaced with a peptide". Does it mean that the peptide has the ability to function as complementary deterrmining region" capable of binding to the particular antigen or just any peptide that is hBNP or hBNP mimic. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-9 in part, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94) and further in view of Mischak et al (US 6162902, DATE-ISSUED: December 19, 2000) in view of Barbas et al (b) (PNAS 92:2529-2533, 1995) and Kini et al (FEBS Letters 375:15-17, 1995).

The instant claims are drawn to an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementarity determining regions (CDR) is replaced with a peptide selected from the group consisting of hBNP, hBNP mimetics, further comprising at least one flanking sequence including at least one amino acid covalently linked to at least one end of the peptide, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab').sub.2 fragment and ScFv fragment, wherein at least a portion of two CDRs are replaced with a peptide, wherein the two CDRs are a CDR3 of a heavy chain and a CDR2 of a heavy chain, wherein the immunoglobulin molecule or fragment thereof is human, wherein the immunoglobulin molecule or fragment thereof is

anti-tetanus toxoid, and a composition comprising an immunoglobulin or fragment thereof and a pharmaceutically acceptable carrier.

Barbas et al (a) teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for example (see page 5, 8, 17, lines 5-33, page 19-20, page 26-27, 28-29, 53, 144, 149). Barbas et al (a) also teach wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab')2 fragment and ScFv fragment, or a full IgG molecule, and a composition comprising such antibodies.

Barbas et al (a) does not teach replacing a CDR with a peptide selected from the group consisting of hBNP peptides and hBNP mimetics, comprising one flanking sequence including at least one amino acid covalently linked to atleast one end of the peptide, wherein the two CDRs are both located on a heavy chain, wherein the CDRs are a CDR3 of a heavy chain and a CDR2 or a heavy chain, wherein the immunoglobulin molecule or fragment thereof is human, anti-tetanus toxoid and a composition comprising an immunoglobulin or fragment thereof and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Mischak et al, Barbas et al (b) and Kini et al.

Mischak et al teach various hBNP peptides and hBNP mimetics that can be replaced as CDRs, including a 108 amino acid precursor that is enzymatically cleaved to yield the mature hBNP peptide. Mature hBNP consists of a 32 amino acid peptide

containing a 17 amino acid ring structure (which is 100% identical to SEQ ID NO:172, the hBNP mimetic peptide used in the instant application) (please see description of the prior art and the summary of the invention, in parituclar).

Barbas et al (b) (introduction, in particular) teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences. Barbas et al (b) also teach the sequence of the anti-tetanus toxoid antibody, wherein the heavy chain CDR2 and CDR3 are replaced.

Kini et al teach design of biologically active peptide with proline residues flanking the sequence and the prolines resulted in restricting the conformation and in enhanced activity of the peptides (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementarity determining regions (CDR) is replaced with a peptide selected from the group consisting of hBNP, hBNP mimetic.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the teachings of Barbas et al (a) because Barbas et al (a) teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking

sequences for presenting a biological active peptide in a conformation for binding to a receptor.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the teachings of Barbas et al (a) and with Mischak et al because Barbas et al (a) teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and because Mischak et al teach various hBNP peptides and hBNP mimetics that can be replaced as CDRs, including a 108 amino acid precursor that is enzymatically cleaved to yield the mature hBNP peptide, wherein mature hBNP consists of a 32 amino acid peptide containing a 17 amino acid ring structure (which is 100% identical to SEQ ID NO:172, the hBNP mimetic peptide used in the instant application).

Moreover, one of ordinary skill in the art would have known that to combine the studies of Barbas et al (a) and with Mischak et al, with Barbas et al (b) because Barbas et al (b) teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences. Barbas et al (b) also teach the sequence of the anti-tetanus toxoid antibody, wherein the heavy chain CDR2 and CDR3 are replaced.

Furthermore, one of ordinary skill in the art would have known would have been motivated and would have had a reasonable expectation of success to have produced a an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementarity determining regions (CDR) is replaced with a peptide as taught by Barbas et al (a); selected from the group consisting of hBNP, hBNP mimetics as taught by Mischak et al; further comprising at

least one flanking sequence including at least one amino acid covalently linked to at least one end of the peptide, wherein the immunoglobulin molecule fragment is selected from the group consisting of Fab fragment, F(ab').sub.2 fragment and ScFv fragment a composition comprising an immunoglobulin or fragment thereof and a pharmaceutically acceptable carrier as taught by Barbas et al (a); wherein at least a portion of two CDRs are replaced with a peptide, wherein the two CDRs are a CDR3 of a heavy chain and a CDR2 of a heavy chain, wherein the immunoglobulin molecule or fragment thereof is human, wherein the immunoglobulin molecule or fragment thereof is anti-tetanus toxoid as taught by Barbas et al (b); and design of biologically active peptide with proline residues flanking the sequence and the prolines resulted in restricting the conformation and

Thus it would have been obvious to one skilled in the art to have produced an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a complementarity determining regions (CDR) is replaced with a peptide selected from the group consisting of hBNP, hBNP mimetic.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Tsuji et al (US Patent 6677124; DATE-ISSUED - January 13, 2004).

2. Sudoh et al (PB PUB 20030162710; PUD Date – August 28th, 003).

3. Clemens et al. 1997. Ameirican Journal of Hypertension. 10:654-661.

4. Mukoyama et al. 1991. J. Clinical Investigation. 87:1402-1412.

Conclusion

10. No claims are allowed

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER